Malignancy and mortality in pediatric patients with inflammatory bowel disease: A multinational study from the porto pediatric IBD group

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Abstract: BACKGROUND: The combination of the severity of pediatric-onset inflammatory bowel disease (IBD) phenotypes and the need for intense medical treatment may increase the risk of malignancy and mortality, but evidence regarding the extent of the problem is scarce. Therefore, the Porto Pediatric IBD working group of ESPGHAN conducted a multinational-based survey of cancer and mortality in pediatric IBD. METHODS: A survey among pediatric gastroenterologists of 20 European countries and Israel on cancer and/or mortality in the pediatric patient population with IBD was undertaken. One representative from each country repeatedly contacted all pediatric gastroenterologists from each country for reporting retrospectively cancer and/or mortality of pediatric patients with IBD after IBD onset, during 2006-2011. RESULTS: We identified 18 cases of cancers and/or 31 deaths in 44 children (26 males) who were diagnosed with IBD (ulcerative colitis, n = 21) at a median age of 10.0 years (inter quartile range, 3.0-14.0). Causes of mortality were infectious (n = 14), cancer (n = 5), uncontrolled disease activity of IBD (n = 4), procedure-related (n = 3), other non-IBD related diseases (n = 3), and unknown (n = 2). The most common malignancies were hematopoietic tumors (n = 11), of which 3 were hepatosplenic T-cell lymphoma and 3 Ebstein-Barr virus-associated lymphomas. CONCLUSIONS: Cancer and mortality in pediatric IBD are rare, but cumulative rates are not insignificant. Mortality is primarily related to infections, particularly in patients with 2 or more immunosuppressive agents, followed by cancer and uncontrolled disease. At least 6 lymphomas were likely treatment-associated by virtue of their phenotype.

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Malignancy and Mortality in Pediatric Patients with Inflammatory Bowel Disease: A Multinational Study from the Porto Pediatric IBD Group

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Results: We identified 18 cases of cancers and/or 31 deaths in 44 children (26 males) who were diagnosed with IBD (ulcerative colitis, n = 21) at a median age of 10.0 years (inter quartile range, 3.0–14.0). Causes of mortality were infectious (n = 14), cancer (n = 5), uncontrolled disease activity of IBD (n = 4), procedure-related (n = 3), other non-IBD related diseases (n = 3), and unknown (n = 2). The most common malignancies were hematopoietic tumors (n = 11), of which 3 were hepatosplenic T-cell lymphoma and 3 Ebstein–Barr virus–associated lymphomas.

Conclusions: Cancer and mortality in pediatric IBD are rare, but cumulative rates are not insignificant. Mortality is primarily related to infections, particularly in patients with 2 or more immunosuppressive agents, followed by cancer and uncontrolled disease. At least 6 lymphomas were likely treatment-associated by virtue of their phenotype.

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Key Words: pediatric inflammatory bowel disease, mortality, cancer, survey

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The incidence of pediatric inflammatory bowel disease (PIBD) in European countries has risen significantly in the past 2 decades, as shown by several recent studies.[1–3] Over this same period, medical treatment of PIBD has changed considerably with a tendency for using more aggressive immunosuppressive medications earlier in the disease course. In addition, pediatric-onset IBD is more often extensive, more severe, and patients have a longer anticipated duration of disease, as compared with adults.[4,5]

Death and cancer from IBD in children are devastating but fortunately rare and may be because of factors related to the inflammation or those related to medical or surgical interventions. Disease-associated cancers are usually adenocarcinomas arising from chronic inflammation, whereas lymphoproliferative disorders (e.g., Ebstein–Barr virus [EBV]–associated lymphomas or hepatosplenic T-cell lymphomas [HSTCL]) have been associated with specific treatments, most notably thiopurines.[6,7] In addition, cervical cancer and skin cancers have been recognized as adverse events of immunosuppressive medications, including biologics. The need to control active disease, decrease steroid exposure, and prevent complications has led to an increased exposure to thiopurines, biologics, and calcineurin inhibitors[8–10] and hesitation to combine biologics and immunomodulators for patients who failed monotherapy.[11] It is difficult to assess the risk of malignancy and mortality in small pediatric clinical trials with short-term follow-up. Therefore, the Porto Pediatric IBD working group of ESPGHAN conducted a multinational–based survey of malignancy and mortality in PIBD to assess the causes of mortality, the types of cancers that occur, and their association to disease-related factors or to medical or surgical interventions.

METHODS

This is a retrospective multinational multicenter study. The choice of a retrospective design was made based on the expected low incidence rate of the outcomes. A 6-year period was chosen, because it is reasonable to assume that recall bias of pediatricians

TABLE 1. National Pediatric Gastroenterologists or Pediatric Gastroenterology Centers Taking Care of Pediatric Patients with IBD with Percentage of Active Response; Patient Numbers (Mortality and/or Cancer) per Country, During 2006–2011

Country	Pediatric Gastroenterologists or Centers Treating Patients with PIBD per Country	Percentage of Pediatric Gastroenterologist Who Actively Replied, %	Total No. of Patients (n = 44)	Mortality Cases per Country	Cancer Cases per Country
Germany	145 ped GIs	70	8	6	3
England	75 ped GIs	NA	4	4	1
Wales	4 ped GIs	100	1	0	1
Scotland	10 ped GIs	100	2	1	2
Spain	115 ped GIs	90	4	3	1
Sweden	21 regions	62	4	3	1
The Netherlands	35 ped GIs	100	3	1	2
Poland	16 centers	100	3	3	1
Greece	15 centers	100	2	2	1
Czech Republic	27 ped GIs	100	2	2	0
Israel	61 ped GIs	69	2	2	0
Finland	15 ped GIs	100	2	1	1
Romania	15 ped GIs	100	2	2	0
Italy	35 ped GIs	94	2	1	1
Croatia	10 centers	100	1	0	1
Hungary	10 centers	100	1	0	1
France	27 centers	44	1	0	1
Belgium	11 centers	100	0	0	0
Switzerland	5 centers	60	0	0	0
Portugal	9 centers	100	0	0	0
Denmark	16 centers	56	0	0	0
Austria	14 ped GIs	50	0	0	0

Ped GI, pediatric gastroenterologist; NA, not available.

TABLE 2. Patient Characteristics of Pediatric IBD Cases Who Developed Cancer Before the Age of 19 Years, During the Period 2006–2011 (n = 18)

	No. of Patients (%)
Gender	
Male	14 (78)
Female	4 (22)
Age at diagnosis of IBD, median (IQR), yr	12 (3–15)
Type of IBD	
CD	12 (67)
UC	4 (22)
IBD-U	1 (6)
Unknown	1 (6)
Disease duration (yr)	5 (2.0–6.0)
Age at diagnosis of cancer, yr	16.0 (14.0–17.0)
Medication (last 3 mo)	
Steroids	4 (22)
Thiopurines	12 (67)
Methotrexate	1 (6)
Biological	2 (11)
Calcineurin inhibitor	1 (6)
Combination therapy (thiopurine and biological)	1 (6)
Medication (any time before 3 mo)	
Steroids	14 (78)
Thiopurines	13 (72)
Biological	2 (11)
Calcineurin inhibitor	1 (6)
Methotrexate	0 (0)
Duration of immunosuppression (mo)	29 (8–60)

Rates or medians (IQR) are presented as appropriate.
IBD-U, inflammatory bowel disease unclassified.

is minimal when probing outcomes such as mortality and cancer within such period.

Dedicated national representatives (1 per country) of 20 European countries and Israel were appointed. The representative contacted all pediatric gastroenterologists within each country through e-mail requesting for possible cases at least twice (unless all pediatric gastroenterologists had already responded on the first e-mail). Besides the e-mails, pediatric gastroenterology colleagues were personally approached during national meetings.

Inclusion criteria for reported cases were patients with IBD diagnosed before 19 years of age, who were diagnosed with any type of malignancy or mortality after disease onset of IBD but before the age of 19 years. To further minimize recall bias, we limited the reported cases to the 6 years preceding the survey (2006–2011).

For each reported case, a form was filled in and collected. A structured form of data ascertainment was completed for each reported case, including questions on patient characteristics, disease history, treatments, comorbidity, type of malignancy, and/or cause of death. In France (EPIMAD) and Germany together with Austria (CEDATA-GPGE), national IBD registries of malignancy and mortality have been identified and explored for further missed cases. Patients reported outside the time frame were excluded from analysis.

RESULTS

The 21 national representatives identified 44 children (18 with malignancy, 31 with mortality of which 5 died because of malignancy) from 15 countries (Table 1). The percentage of the national pediatric gastroenterology colleagues who actively responded whether they had had any cases is recorded in Table 1. Furthermore, the national representatives assumed, because of personal communication during meetings, that all pediatric gastroenterologists who did not respond to the e-mails did not have any patients fitting the inclusion criteria. The exploration of the national databases EPIMAD and CEDATA-GPGE did not reveal any additional cases. In the years 2006–2011; 7, 6, 4, 5, 3, and 16 cases have been reported, respectively. The precise year of mortality or development of cancer or mortality was unknown in 3 cases.

Malignancy

Patient characteristics and details of the 18 children developing a malignancy are shown in Tables 2 and 3, respectively. The majority of patients (67%) had Crohn's disease (CD). Eleven out of 18 (61%) had developed a lymphoma or leukemia of which 3 were HSTCL and 3 EBV-positive lymphomas, which are typically associated with immunosuppression. These 6 patients had all been treated with thiopurines (ranging from 12 to 96 mo) until diagnosis, but one who had stopped thiopurines at least 3 months before HSTCL was diagnosed. Only 1 patient had also received 3 infliximab infusions, 5 years before the diagnosis of cancer. One patient with ulcerative colitis (UC) developed an adenocarcinoma of the colon at 16 years of age after a disease duration of 13 years. He had been diagnosed of UC at 3 years and of primary sclerosing cholangitis at 13 years of age. Another patient with UC developed cholangiocarcinoma at the age of 8 years, with a disease duration of 5 years, without known primary sclerosing cholangitis. Of those who died due to a malignancy, 4 out of 5 malignancies are likely associated with IBD or the treatment received (HSCTL [n = 2], EBV-positive lymphoma [n = 1], and 1 adenocarcinoma).

All 3 patients who developed HSTCL were males and had exposure to thiopurines ranging from 32 to 108 months; none received a biologic. Two of the 3 EBV-associated lymphomas received thiopurines before diagnosis, whereas the medical therapy for the third patient was not available.

Mortality

We identified 31 fatalities among patients during follow-up, and patient characteristics and details are shown in Tables 4 and 5, respectively. The majority of patients (61%) had UC.

TABLE 3. Reported Pediatric IBD Cases Who Developed Cancer Before the Age of 18 Years, During the Period 2006–2011 (n = 18)

	Age at Diagnosis of IBD (yr)/Sex, Type of IBD	Type of Cancer	Age at Development of Cancer (yr)	Mortality	Immunosuppressants Last 3 mo (Duration)/Other Drugs	Biologicals Last 3 mo (Duration)	Calcineurin Inhibitor Last 3 mo (Duration)
1	3/F, UC	Cholangiocarcinoma	8	No	Thiopurine (18)	No	No
2	2/M, UC	HSTCL	9	No	Steroids, thiopurine (72)	No	No
3	12/F, CD	Acute lymphoid leukemia	13	No	Steroids, thiopurine (12)	No	No
4	8/M, CD	Primitive neuroectodermal tumor	14	Yes	Steroids, thiopurine (12)	No	Yes (9)
5	2/M, IBD-U	HSTCL	15	Yes	Thiopurine (108), sulfasalazine	No	Yes (18)
6	10/M, CD	EBV-associated lymphoma	15	Yes	Steroids, thiopurine (12)	No	Yes (25)
7	15/M, CD	Acute myeloid leukemia	15	No	Thiopurine (10)	No	No
8	14/M, CD	Medulloblastoma	15	No	No	Yes (18)	No
9	10/F, CD	Pilocytic astrocytoma of cerebellum	15	No	Methotrexate (30)	No	No
10	3/M, UC	Adenocarcinoma of colon	16	Yes	Steroids, thiopurine (240)	Yes (24)	Yes (16)
11	15/M, CD	Hodgkin's lymphoma	16	No	Thiopurine (2)	No	No
12	15/M, CD	EBV-positive Hodgkin-like lymphoma	16	No	Thiopurine (21)	No	No
13	12/M, CD	Hodgkin lymphoma	16	No	Thiopurine (48)	No	No
14	9/M, CD	EBV-associated lymphoma	17	No	Thiopurine (96)	Unknown	Unknown
15	14/M, CD	Basal cell carcinoma	17	No	No	Yes (24)	No
16	17/M, CD	Hodgkin lymphoma	17	No	Thiopurine (3)	No	No
17	16/M, CD	Chromophobic renal carcinoma	17	No	Steroids, mesalamine	No	No
18	15/M, CD	HSTCL	18	Yes	Steroids, thiopurine (32)	No	Yes (8)

IBD-U, inflammatory bowel disease unclassified.

TABLE 4. Patient Characteristics of Pediatric Patients with IBD Who Died (Total n = 31)

	No. of Patients (%)
Gender	
Male	17 (55)
Female	14 (45)
Age at diagnosis IBD, median (IQR), yr	8.9 (3–14)
Type of IBD	
CD	9 (29)
UC	19 (61)
IBD-U	2 (6)
Unknown	1 (3)
Disease duration, median (IQR), yr	3.0 (2.0–8.0)
Age at moment of death, median (IQR), yr	14.6 (13.1–16.0)
Cause of death	
Infection	14 (45)
Cancer	5 (16)
Other disease	3 (10)
Uncontrolled disease activity	4 (13)
Procedure-related complication	3 (10)
Unknown	2 (6)
Medication (last 3 mo)	
Steroids	19 (61)
Thiopurines	18 (58)
Methotrexate	2 (6)
Biological	8 (26)
Calcineurin inhibitor	7 (23)
Combination therapy	19 (61)
Medication (previous)	
Steroids	25 (81)
Thiopurines	21 (68)
Methotrexate	6 (19)
Biological	8 (26)

IBD-U, inflammatory bowel disease unclassified.

The underlying cause for the infectious-related mortality cases (n = 14) included sepsis (n = 7, 47%) and opportunistic infections (n = 4, 29%), such as candida and varicella virus. Cases of tuberculosis or *Pnarmocystis jimveci* pneumonia were not diagnosed.

Medications used in the 3 months preceding mortality of the 14 children who died because of infectious causes were given monotherapy with steroids (n = 1, 7%) or thiopurine (n = 1, 7%), combination therapy of 2 immunomodulators (n = 11, 73%) (steroids and thiopurine [n = 4], steroids and MTX [n = 1], steroids and biologic [n = 1], thiopurine and biologic [n = 2], MTX and biologic [n = 1], and thiopurine and calcineurin inhibitor [n = 2]) or combination therapy of even 4 immunomodulators (n = 1, 7%) (steroids, thiopurine, biologic, and a calcineurin inhibitor).

Three out of the 14 patients (21%) were treated with total parenteral nutrition through a central venous access. All these patients had CD and had been treated with a biologic, in combination with either steroids, thiopurine, or MTX.

Three out of 5 patients who died due to cancer were probably treatment-related, these resulted from HSTCL (n = 2) and EBV-positive lymphoma (n = 1). One patient died due to a malignancy, which probably was disease-related, being colonic adenocarcinoma. The fifth patient had a primitive neuroectodermal tumor.

Four patients died because of uncontrolled disease activity as follows: 1 patient died because of complications of CD, which were not further specified; 1 patient developed toxic megacolon and sepsis; and 1 multiorgan failure (we could not ascertain if sepsis was present). The latter 2 patients were nonadherent to their medication. The fourth patient developed cardiomyopathy and a fatal thromboembolic event.

Three patients died because of procedure-related complications, including a perforation during surgical colectomy to treat toxic megacolon, pericardial tamponade during anesthesia, and a sepsis and cerebral thrombosis, shortly after total colectomy.

DISCUSSION

In the era of increased use of biologics and immunosuppressive medications, development of management strategies for IBD requires evidence for an effect of treatment and adverse outcomes, so that risk/benefit can be applied to the decision making process by clinicians. Biologics and immunosuppressants are used in combination quite frequently, whether combination therapy is superior to any individual therapy is still a matter of debate.[12] Recent large studies have shown that early immunosuppression decreases the risk for stricturing and penetrating disease and the need for surgery over 10 years of follow-up.[13] Although data regarding the risk for disease-associated complications such as stricturing, penetrating, or perianal disease are available, data regarding the risk for the most severe complications such as cancer and fatal disease are still lacking in children.

Malignancy

At least 6 lymphomas (HSTCL or EBV-positive lymphoma) were likely treatment-associated, by virtue of their phenotype. Pediatricians using immunosuppressants (typically thiopurines often in combination with anti-TNFs, although the patients developing HSTCL or EBV-positive lymphoma within this cohort were all treated with thiopurine monotherapy) should be aware of this rare but very serious complication.

Disease-related malignancies were likely in 2 patients who developed adenocarcinomas of the gastrointestinal tract. The third most common malignancy after HSTCL and EBV-positive lymphoma was Hodgkin lymphoma, which is common in adolescents regardless of IBD. The lack of a control group makes it impossible to elucidate how many of the Hodgkin cases are disease-specific.

TABLE 5. Pediatric IBD Cases Who Died Before the Age of 18 Years During the Period 2006–2011 (n = 31)

	Age at Diagnosis of IBD (yr)/Sex, Type of IBD	Cause of Mortality	Age at Death, yr	Immunosuppressants and Steroids Last 3 mo (Duration)/Other Drugs	Biologicals Last 3 mo (Duration)	Calcineurin Inhibitor Last 3 mo (Duration)
1	1/M, UC	Decompensation of maple syrup disease, neurological complications, multiorgan failure	2	Steroids, thiopurine 4)	No	Yes (2)
2	3/M, UC	Toxic megacolon, sepsis. Nonadherence to medication	5	Mesalamine	No	No
3	2/M, UC	Shock and severe dehydration, cause unknown	5	Steroids, thiopurine (2), antibiotics	No	No
4	7/F, UC	Sepsis	8	Steroids, thiopurine (6)	No	No
5	7/F, UC	Acute myocarditis	9	Steroids, granulocyte aferesis	No	No
6	2/F, CD	Complications of CD	10	Steroids, thiopurine (>3), methotrexate	Yes (duration unknown)	Yes (duration unknown)
7	0.5/M, IBD-U	Sepsis	13	Steroids, total parenteral nutrition, antibiotics	No	No
8	9/F, UC	Chickenpox	13	Steroids, thiopurine (48)	No	Yes (24)
9	5/M, CD	*E. coli* and candida sepsis (CVL)	13	Steroids, thiopurine	Yes (>3)	No
10	6/F, UC	Postoperative complication after colectomy	14	Steroids	No	No
11	8/M, CD	Primitive neuroectodermal tumor	14	Steroids, thiopurine (12)	No	No
12	14/F, UC	Ventricular fibrillation, cause unknown	14	Steroids, thiopurine (>3)	No	No
13	14/F, UC	Toxic megacolon, perforation	14	Steroids, antibiotics	No	No
14	10/M, CD	Multiorgan failure, malnutrition, intracranial ischemia. Nonadherence to medication	14	Steroids, mesalamine, ursodeoxycholic acid, probiotics	No	No
15	11/F, CD	Pericardial tamponade during anesthesia	14	Steroids, thiopurine (>3)	Yes (duration unknown)	Yes (<3)
16	7/M, UC	Uncontrolled diarrhea, exact cause of death unknown	14	Steroids, thiopurine (2), mesalamine	No	No
17	2/M, IBD-U	HSTCL	15	Thiopurine (108), sulfasalazine	No	No
18	13/M, UC	Sepsis	15	Steroids, thiopurine (6) antibiotics	Yes (1 dose)	Yes (1)
19	12/F, UC	Meningitis	15	Steroids, thiopurine (36)	No	Yes (12)
20	12/F, UC	ARDS (pneumonia), CMV colitis, and CMV-pneumonia	15	Steroids, thiopurine (>3), ganciclovir	No	Yes (duration unknown)
21	10/M, CD	EBV-associated lymphoprolipherative disease	15	Steroids, thiopurine (12)	No	No
22	14/F, CD	Multiorgan failure	16	Thiopurine (>3), mesalamine	No	No
23	14/F, UC	Bronchopneumonia, possibly related to morphine use and aspiration	16	Steroids, thiopurine (>3)	Yes (>3)	No
24	3/M, UC	Adenocarcinoma of colon	16	Steroids, thiopurine (240)	Yes (48)	Yes (24)
25	3/M, CD	Sepsis, intracranial hemorrage	16	Steroids, thiopurine (unknown), total parenteral nutrition, antbiotics	No	No
26	8/M, CD	Staph coag neg sepsis (CVL), pulmonary aspergillus	16	Thiopurine (>3), total parenteral nutrition	Yes (duration unknown)	No

TABLE 5 (*Continued*)

	Age at Diagnosis of IBD (yr)/Sex, Type of IBD	Cause of Mortality	Age at Death, yr	Immunosuppressants and Steroids Last 3 mo (Duration)/Other Drugs	Biologicals Last 3 mo (Duration)	Calcineurin Inhibitor Last 3 mo (Duration)
27	16/M, UC	Cardiomyopathy, thromboembolism	16	Steroids	No	No
28	15/M, UC	Progression of Duchenne	17	Steroids, thiopurine (unknown), sulfasalazine	No	No
29	15/F, UC	Postoperative complication after colectomy (sepsis and thromboembolism)	17	Thiopurine (24) steroids	Yes (2)	Yes (7)
30	9/F, UC	EBV-associated hemophagocytic lymphohistiocytosis	18	Steroids, thiopurine (>3)	No	No
31	15/M, CD	HSTCL	18	Steroids, thiopurine (32)	No	No

CVL, central venous line; ARDS, acute respiratory distress syndrome; CMV, cytomegalovirus; IBD-U, inflammatory bowel disease unclassified; Staph coag neg sepsis, coagulase-negative staphylococcal sepsis.

Interestingly enough, none of the malignancy-associated fatalities occurred during the use of a biologic. This may reflect the less frequent use and access in pediatric patients to biologics during the study period.

Although assuming significant underreporting bias (see limitations), IBD-associated malignancies seem rare. This probably reflects age-related risk, but also that disease- and therapy-associated malignancies require prolonged exposure to inflammation or drugs to occur. This was illustrated in a systematic review on the natural history of pediatric-onset IBD,[14] showing that cancers were reported in only 14 patients within 11 clinic/hospital-based studies. Twelve out of these 14 (86%) patients developed cancer after the age of 19 years. Six out of the 14 patients had CD, and they all developed colonic or small bowel adenocarcinoma except one who developed metastatic breast carcinoma, whereas 8 out of the 14 patients had UC, and they all developed colonic adenocarcinoma except one who developed cholangiocarcinoma.

The CESAME study on lymphoproliferative disorders in patients with IBD found an incidence of 9 per 10,000 patient-years among 5867 patients treated with thiopurines, most were the EBV-positive lymphoproliferative type.[15] The maximum risk was associated with older age and longer duration of disease.

A large Dutch study in 17,834 patients with IBD identified 44 lymphomas (only adult patients, diagnosed at mean age of 54 yr, only 1 patient with pediatric-onset CD at age of 17 yr), resulting in a relative risk of 1.27 (95% confidence interval, 0.92–1.68).[16] Nineteen of 44 patients (43%) were exposed to thiopurines. A total of 92% of patients (11/12) with EBV-positive lymphoma were treated with thiopurines compared with only 19% patients (4/21) with EBV-negative lymphoma, suggesting a strong relation between EBV-positive lymphoma and thiopurine use. This is in accordance with the EBV-positive lymphoma cases in our study cohort. Although there is evidence that IBD therapies in adult patients increase the risk of certain malignancies in patients with both CD and UC (lymphomas, HSTCL, and non melanoma skin cancer), the absolute incidence rate of these malignancies is low.[17] For example, the absolute incidence of non-Hodgkin's lymphoma is estimated to be 6.1 per 10,000 patient-years while on combination therapy of an immunosuppressor and anti-TNF in patients with CD in a meta-analysis.[18] Male patients under 35 years seem to be at particular risk of HSTCL, especially when exposed to either a thiopurine or thiopurine in combination with anti-TNF therapy. However, the estimated absolute risk for men <35 years on combination therapy still is extremely low, being 1:3534.[19] The data from our study also seem to show that the risk is low, because only 3 patients with HSTCL were identified during a 6-year period in 20 countries, although thiopurine use was common during this time period.

In children, the risk for these malignancies seems even lower, but it is unknown whether it increases with age. A retrospective study on children and young adults with IBD found only 2 cases of lymphomas during childhood (males at age 12 and 18 yr, both treated with thiopurines) among 1374 patients with a mean follow-up of 4.8 years.[20] The incidence among thiopurine-exposed patients

was 4.5 per 10,000 patient-years. These findings demonstrate that fatal events are rare during childhood. However, the life-time risk is unknown, and thus the question to what extent drug-related risk should dominate treatment decisions in this age group remains unanswered.

Mortality

We found that mortality is uncommon and is primarily related to the occurrence of infections. It is striking that the majority of patients were diagnosed with UC, although UC is considered to be curable by colectomy. Nine out of 19 (47%) patients with UC died because of an infectious complication. These fatalities may have been prevented by earlier surgical intervention when intensified medical treatment is ineffective (Fig. 1). In addition, this could serve as an argument against sequential therapy in acute severe colitis (calcineurin inhibitors after infliximab or vice versa) instead of colectomy, as suggested in the recent ECCO/ESPGHAN guideline.[21]

Most of the patients with fatal infections were treated with 2 or more immunomodulators (n = 12, 86%), although this was only the case for 1 patient who developed cancer and for 6 (35%) patients who died because of causes other than infections. This illustrates the increased risk of infectious complications in patients on combination of immunomodulatory therapy.[22] Three of these 13 patients were at risk of infections by virtue of a central venous catheter. Whenever possible, enteral instead of parenteral nutrition should be used because a central venous catheter in immune-suppressed patients clearly is a risk.

To prevent opportunistic infections in children with IBD on immunosuppressive therapy, the recently published guidelines should be followed.[23,24] These guidelines include assessment and correction of the patient's nutritional status because malnutrition is a concomitant risk factor for an opportunistic infection and optimization of immunizations before the initiation of immuno-suppressive agents. For children with triple immunosuppressive therapy, cotrimoxazole prophylaxis against *P. jiroveci* is advised.

Limitations

This report is the first to assess major risks of PIBD in a large population, but it is not without limitations. The first limitation is the retrospective design of the study. It is almost certain that the reported cases are not a full list of fatalities and cancer in the included countries during the study period, but it is impossible to assess the rate of underreporting. Physicians treating pediatric patients with IBD may not have been contacted or may have not cooperated, but patients may have been treated by adult gastroenterologists at an age younger than 19 years as shown in the EUROKIDS registry, which makes it likely that many patients with IBD from the age of 15 years are diagnosed and treated by adult gastroenterologists.[25]

We could not calculate if children with IBD were at increased risk for cancer or mortality because of the lack of a denominator (the number of children with IBD in each country and the risk for mortality in the underlying population).

Patients who died of other causes and did not show up for follow-up may have been missed because of lack of awareness. An additional limitation has to do with the age limitations within the study design. We assessed the burden of serious adverse outcome by the age of 19 years. However, it is plausible to assume that many developed a malignancy or died after that age,

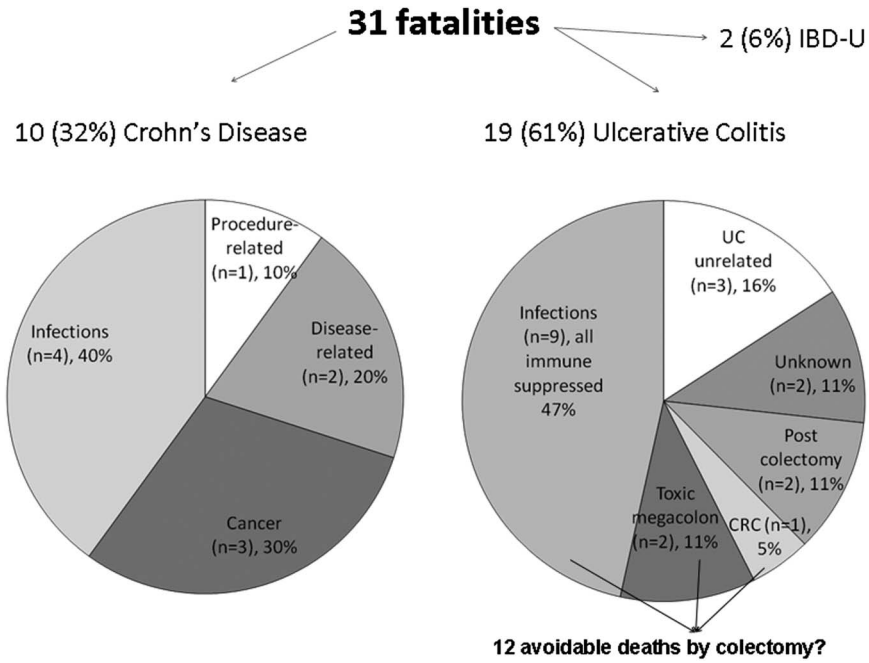

FIGURE 1. Causes of fatalities in pediatric IBD. IBD-U, inflammatory bowel disease unclassified.

which still could be a consequence of the disease or treatment prescribed during childhood. In addition, we did not ascertain the denominator of treated PIBD during the same period. However, it was not the aim of the study to elucidate exact rates of adverse events but to bring to the attention of practicing gastroenterologists that serious adverse events of both the disease and treatment do occur and to highlight the ratio between these 2 competing groups. Although we do not know how many of the cancer cases are unrelated to the disease, at least 6 of the reported malignancies were clearly related to the disease or its treatment and probably some of the others also.

Taken together, the true case ascertainment of grave outcomes during childhood is probably higher than reported here. First, it is important to note that at least half of mortality cases reported were treatment-related, whereas approximately 1/6 were disease-related and 1/10 were procedure-related. Second, only 2 cases of mortality were because of surgical complications in UC, and more were related to uncontrolled disease or immunosuppressant treatment. However, more patients will have received medical than surgical treatment, which makes these numbers difficult to compare head-to-head. Still, it seems important to consider colectomy in every case of resistant disease requiring multiple immunosuppressant medications.[26]

Many recent studies have focused on specific outcomes such as surgery, infection, or lymphomas; and depending on the outcome, advocate either earlier immunomodulation to prevent complicated disease and surgery or less immunomodulation to prevent medication-associated adverse events. Reports that just focus on cancer but not on severe disease outcome induce a bias. Because there is a lack of evidence-based guidance, physicians need to weigh all the different risks and propose a comprehensive strategy for young patients with a severe disease burden.[15,21]

We clearly need larger cohorts with prospective data collection to understand the risk of withholding treatment versus overtreatment, and this report should be regarded as a preliminary attempt to address the complex problem of the very rare but severe outcomes of PIBD.

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REFERENCES

1. Martín-de-Carpi J, Rodríguez A, Ramos E, et al; SPIRIT-IBD Working Group of SEGHNP (Sociedad Española de Gastroenterología, Hepatología y Nutrición Pediátrica). Increasing incidence of pediatric inflammatory bowel disease in Spain (1996-2009): The SPIRIT registry. *Inflamm Bowel Dis.* 2013;19:73–80.
2. Lehtinen P, Ashorn M, Iltanen S, et al. Incidence trends of pediatric inflammatory bowel disease in Finland, 1987-2003, a nationwide study. *Inflamm Bowel Dis.* 2011;17:1778–1783.
3. Henderson P, Hansen R, Cameron FL, et al. Rising incidence of pediatric inflammatory bowel disease in Scotland. *Inflamm Bowel Dis.* 2012;18:999–1005.
4. Van Limbergen J, Russell RK, Drummond HE, et al. Definition of phenotypic characteristics of childhood-onset inflammatory bowel disease. *Gastroenterology.* 2008;135:1114–1122.
5. Levine A. Pediatric inflammatory bowel disease: is it different? *Dig Dis.* 2009;27:212–214.
6. Thai A, Prindiville T. Hepatosplenic T-cell lymphoma and inflammatory bowel disease. *J Crohns Colitis.* 2010;4:511–522.
7. Sebastian S, Hernández V, Myrelid P, et al. Colorectal cancer in inflammatory bowel disease: results of the 3rd ECCO pathogenesis scientific workshop (I). *J Crohns Colitis.* 2014;8:5–18.
8. Brackmann S, Andersen SN, Aamodt G, et al. Two distinct groups of colorectal cancer in inflammatory bowel disease. *Inflamm Bowel Dis.* 2009;15:9–16.
9. Piton G, Cosnes J, Monnet E, et al. Risk factors associated with small bowel adenocarcinoma in Crohn's disease: a case-control study. *Am J Gastroenterol.* 2008;103:1730–1736.
10. Palascak-Juif V, Bouvier AM, Cosnes J, et al. Small bowel adenocarcinoma in patients with Crohn's disease compared with small bowel adenocarcinoma de novo. *Inflamm Bowel Dis.* 2005;11:828–832.
11. Bern EM, Bousvaros A. Loss of response to biologics versus increased risk of lymphoma in children with inflammatory bowel disease: the clinician's conundrum. *Expert Rev Clin Immunol.* 2013;9:117–127.
12. Colombel JF, Sandborn WJ, Reinisch W, et al; SONIC Study Group. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med.* 2010;362:1383–1395.
13. Vernier-Massouille G, Balde M, Salleron J, et al. Natural history of pediatric Crohn's disease: a population-based cohort study. *Gastroenterology.* 2008;135:1106–1113.
14. Abraham BP, Mehta S, El-Serag HB. Natural history of pediatric-onset inflammatory bowel disease: a systematic review. *J Clin Gastroenterol.* 2012;46:581–589.
15. Beaugerie L, Brousse N, Bouvier AM, et al; CESAME Study Group. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. *Lancet.* 2009;374:1617–1625.
16. Vos AC, Bakkal N, Minnee RC, et al; Initiative on Crohn's and Colitis (ICC). Risk of malignant lymphoma in patients with inflammatory bowel diseases: a Dutch nationwide study. *Inflamm Bowel Dis.* 2011;17:1837–1845.
17. Mason M, Siegel CA. Do inflammatory bowel disease therapies cause cancer? *Inflamm Bowel Dis.* 2013;19:1837–1845.
18. Siegel CA, Marden SM, Persing SM, et al. Risk of lymphoma associated with combination anti-tumor necrosis factor and immunomodulator therapy for the treatment of Crohn's disease: a meta-analysis. *Clin Gastroenterol Hepatol.* 2009;7:874–881.

19. Kotlyar DS, Osterman MT, Diamond RH, et al. A systematic review of factors that contribute to hepatosplenic T-cell lymphoma in patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol.* 2011;9:36–41.
20. Ashworth LA, Billett A, Mitchell P, et al. Lymphoma risk in children and young adults with inflammatory bowel disease: analysis of a large single-center cohort. *Inflamm Bowel Dis.* 2012;18:838–843.
21. Turner D, Levine A, Escher JC, et al; European Crohn's and Colitis Organization, European Society for Paediatric Gastroenterology, Hepatology, and Nutrition. Management of pediatric ulcerative colitis: joint ECCO and ESPGHAN evidence-based consensus guidelines. *J Pediatr Gastroenterol Nutr.* 2012;55:340–361.
22. Lichtenstein GR, Feagan BG, Cohen RD, et al. Serious infection and mortality in patients with Crohn's disease: more than 5 years of follow-up in the TREAT™ registry. *Am J Gastroenterol.* 2012;107:1409–1422.
23. Rahier JF, Ben-Horin S, Chowers Y, et al; European Crohn's and Colitis Organisation (ECCO). European evidence-based Consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis.* 2009;3:47–91.
24. Veereman-Wauters G, de Ridder L, Veres G, et al; ESPGHAN IBD Porto Group. Risk of infection and prevention in pediatric patients with IBD: ESPGHAN IBD Porto Group commentary. *J Pediatr Gastroenterol Nutr.* 2012;54:830–837.
25. de Bie CI, Buderus S, Sandhu BK, et al; EUROKIDS Porto IBD Working Group of ESPGHAN. Diagnostic workup of paediatric patients with inflammatory bowel disease in Europe: results of a 5-year audit of the EUROKIDS registry. *J Pediatr Gastroenterol Nutr.* 2012;54:374–380.
26. Turner D, Travis SP, Griffiths AM, et al; European Crohn's and Colitis Organization, Porto IBD Working Group, European Society of Pediatric Gastroenterology, Hepatology, and Nutrition. Consensus for managing acute severe ulcerative colitis in children: a systematic review and joint statement from ECCO, ESPGHAN, and the Porto IBD Working Group of ESPGHAN. *Am J Gastroenterol.* 2011;106:574–588.